Traversing the valley of glycemic control despair

From Misplaced Hope to the Valley of Despair, … and Back To Informed Optimism?

J. Geoffrey Chase, Jennifer L. Dickson, Balazs Benyo

Glycemic Control (GC) today in one (1) word

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Contentious

- Or via Google Translate:

Vitás

- Today's Goals:
  - **Is GC valuable?**
  - **What are the needs? … or … Why hasn't it succeeded?**
  - **How to provide safe, effective GC to nearly all patients?**

  - **Talk available at: http://tinyurl.com/ycwwjkvl**
  - **All references (N=32) available at: http://tinyurl.com/yanndo82**

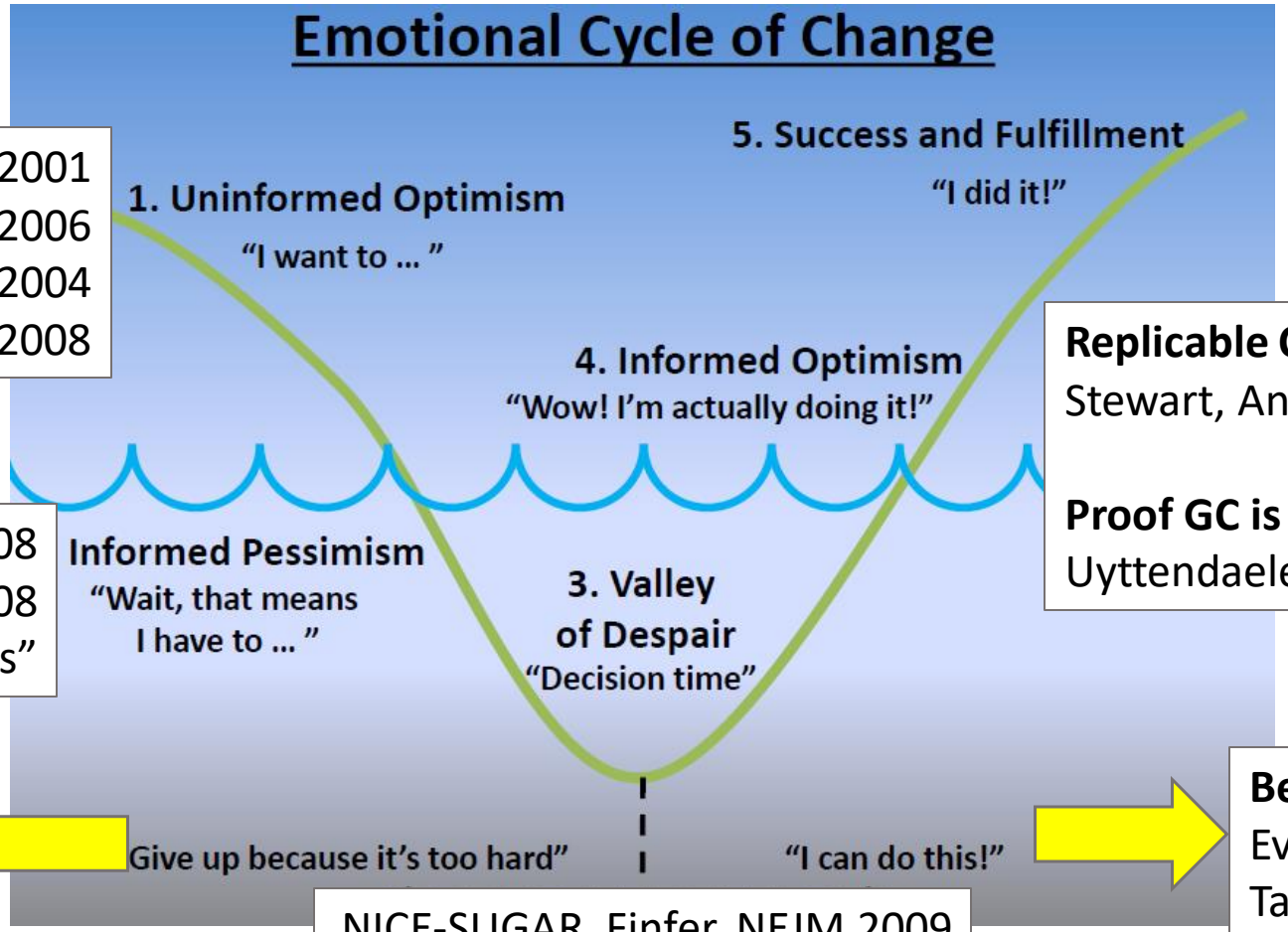
Overview: The Valley of Despair (Kelley and Connor 1979)

Traversing the valley of glycemic control despair

J. Geoffrey Chase* and Jennifer L. Dickson

Chase and Dickson *Critical Care* (2017) 21:237
DOI 10.1186/s13054-017-1824-9

Critical Care



Van den Berghe, NEJM 2001
Van den Berghe, NEJM 2006
Krinsley, May Clin Proc 2004
Chase, Critical Care 2008

Preiser, Int Care Med 2008
Brunkhorst, Int Care Med 2008
Many other "no results"

Higher BG Targets
Ichai, Critical Care 2010
Moghissi, Diabetes Care 2009

NICE-SUGAR, Finfer, NEJM 2009

Replicable Control as Std of Care
Stewart, Annals ICU 2010

Proof GC is the *cause* not the *effect*
Uyttendaele, Critical Care 2017

Better Control
Evans, Annals ICU 2010
Tanenberg, Endo Prac 2017

Positive Associations: Mortality, Morbidity, Cost

Association Between Hyperglycemia and Increased Hospital Mortality in a Heterogeneous Population of Critically Ill Patients

JAMES STEPHEN KRINSLEY, MD

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Organ failure and tight glycemic control in the SPRINT study

J Geoffrey Chase[1*], Christopher G Pretty[1], Leesa Pfeifer[2], Geoffrey M Shaw[3], Jean-Charles Preiser[4],

Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control*

Greet Van den Berghe, MD, PhD; Pieter J. Wouters, MSc; Roger Bouillon, MD, PhD; Frank Weekers, MD;

Metabolic, Endocrine, and Immune Effects of Stress Hyperglycemia in a Rabbit Model of Prolonged Critical Illness

FRANK WEEKERS, ANNA-PAULA GIULIETTI, MARINA MICHALAKI, WILLY COOPMANS,

Glycemic Levels in Critically Ill Patients: Are Normoglycemia and Low Variability Associated with Improved Outcomes?

Matthew Signal, B.E.(Hons.),[1] Aaron Le Compte, Ph.D.,[1] Geoffrey M. Shaw, Mb.Ch.B., FJFICM,[2]

Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults

James S Krinsley[1*] and Jean-Charles Preiser[2]

Glucose control positively influences patient outcome: A retrospective study

Sophie Penning, MSc [a,*], Chris Pretty, PhD [b], Jean-Charles Preiser, PhD [c], Geoffrey M. Shaw,

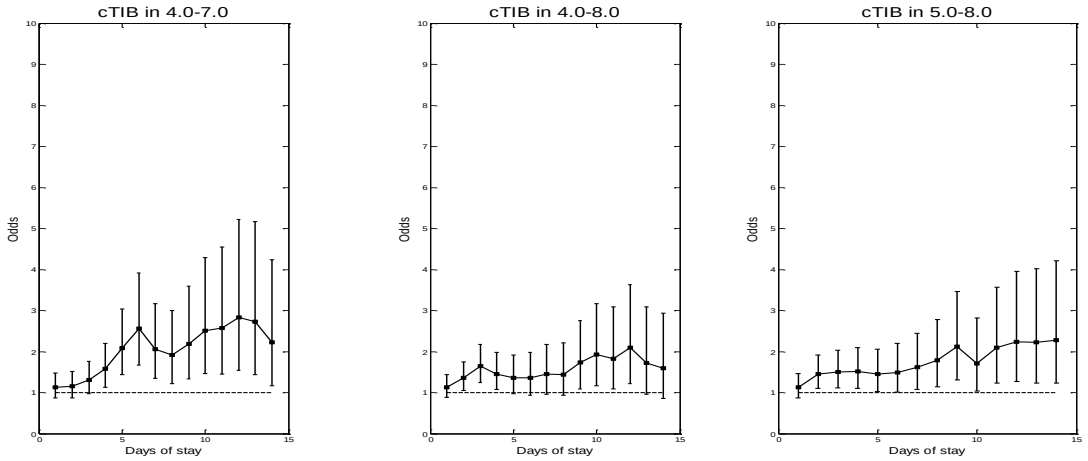
Cost Analysis of Intensive Glycemic Control in Critically Ill Adult Patients*

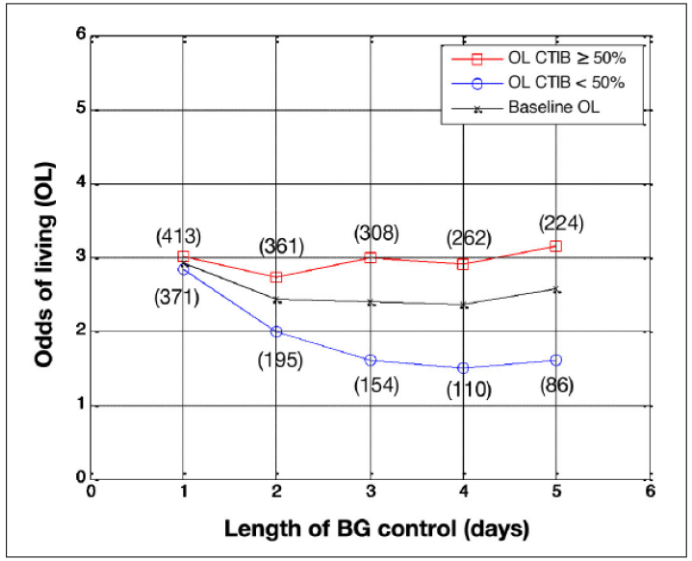
James Stephen Krinsley, MD, FCCP; and Richard L. Jones

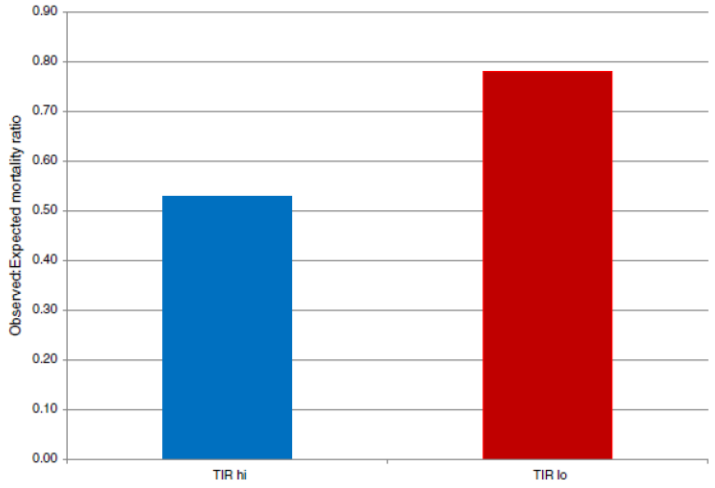
Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients*

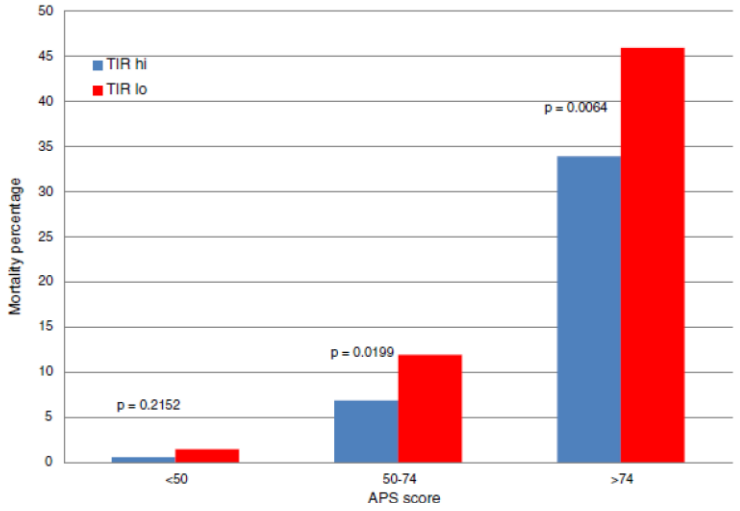
Greet Van den Berghe, MD, PhD; Pieter J. Wouters, MSc; Katrien Kesteloot, PhD; Daniel E. Hilleman, PharmD

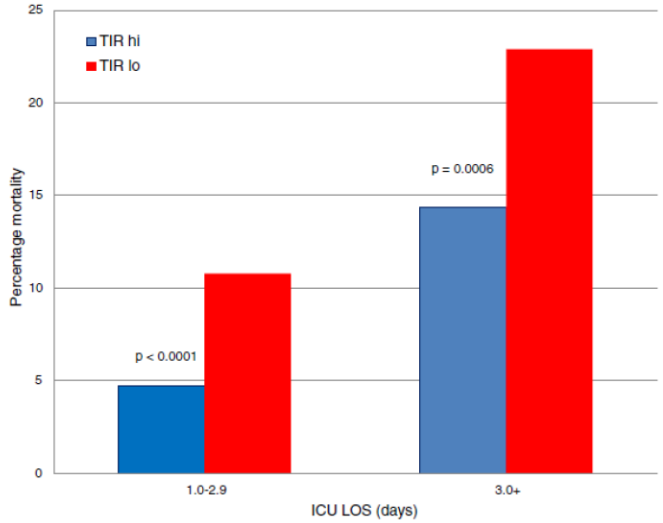
Positive Associations: Mortality, Morbidity, Cost











The Negative Associations: Hypos + Variability

Association Between Hyperglycemia and Increased Hospital Mortality in a Heterogeneous Population of Critically Ill Patients

JAMES STEPHEN KRINSLEY, MD

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Glycemic Variability and Mortality in Critically Ill Patients: The Impact of Diabetes

James Stephen Krinsley M.D., FCCM, FCCP

Journal of Diabetes Science and Technology
Volume 3, Issue 6, November 2009

Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients

Moritoki Egi, M.D., Rinaldo Bellomo, M.D., F.J.F.I.C.M.,† Edward Stachowski, M.D.,‡*

Anesthesiology 2006; 105:244–52

Severe hypoglycemia in critically ill patients: Risk factors and outcomes*

James S. Krinsley, MD, FCCM, FCCP; Aarti Grover, MD

Hypoglycemia and Risk of Death in Critically Ill Patients

The NICE-SUGAR Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

The impact of early hypoglycemia and blood glucose variability on outcome in critical illness

Sean M Bagshaw[1,2], Rinaldo Bellomo[2,3], Michael J Jacka[1,4], Moritoki Egi[5], Graeme K Hart[2,3],

Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients

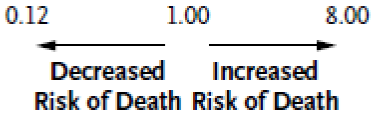
Critical Care (2015) 19:153

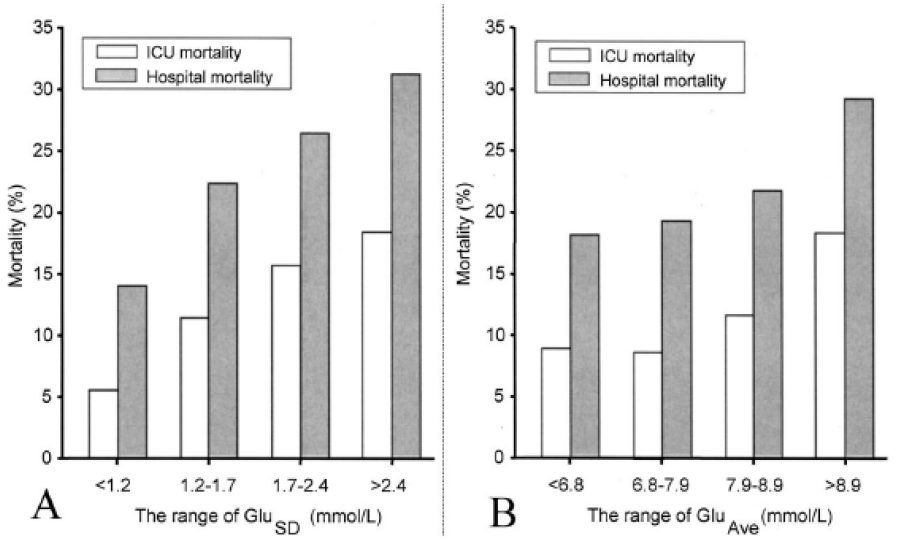
Hypoglycemia and Outcome in Critically Ill Patients

MORITOKI EGI, MD; RINALDO BELLOMO, MD; EDWARD STACHOWSKI, MD; CRAIG J. FRENCH, MD;

The Negative Associations: Hypos + Variability

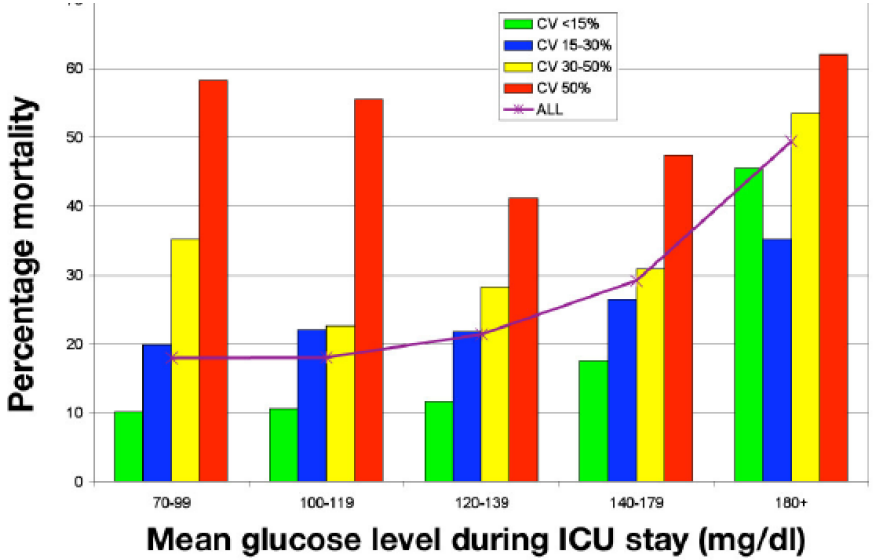
Subgroup	Deaths	Population	Median Time from Hypoglycemia to Death (IQR)	Hazard Ratio (95% CI)	P Value
	no.		*days*		
No hypoglycemia	726	3089		1.00	
Moderate hypoglycemia					0.007
Insulin	545	2066	9 (3–23)	1.22 (1.03–1.44)	
No insulin	136	378	5 (1–22)	1.64 (1.34–2.01)	
Severe hypoglycemia					0.003
Insulin	57	186	10 (4–15)	1.68 (1.23–2.29)	
No insulin	22	37	1 (0–9)	3.84 (2.37–6.23)	



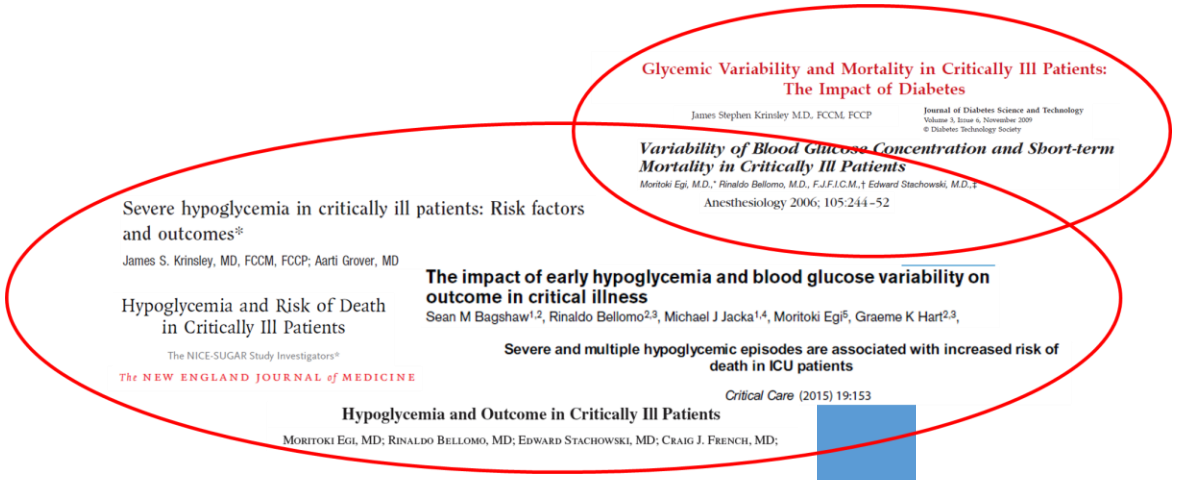


Adjusted ICU and hospital mortality by severity of hypoglycemia in patients with a primary septic diagnosis

Blood glucose category (mmol/L)	ICU mortality Adjusted OR§ (95% CI)	Hospital mortality Adjusted OR‡ (95% CI)
<2.0	4.8 (3.3 to 7.0)	3.8 (2.6 to 5.6)
2.1–2.4	2.4 (1.6 to 3.6)	2.1 (1.4 to 3.1)
2.5–2.9	1.9 (1.4 to 2.6)	1.7 (1.3 to 2.4)
3.0–3.4	2.0 (1.5 to 2.5)	1.8 (1.4 to 2.3)
3.5–3.9	1.3 (1.0 to 1.6)	1.3 (1.0 to 1.6)
4.0–4.4	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)
≥ 4.5¶	1.0	1.0

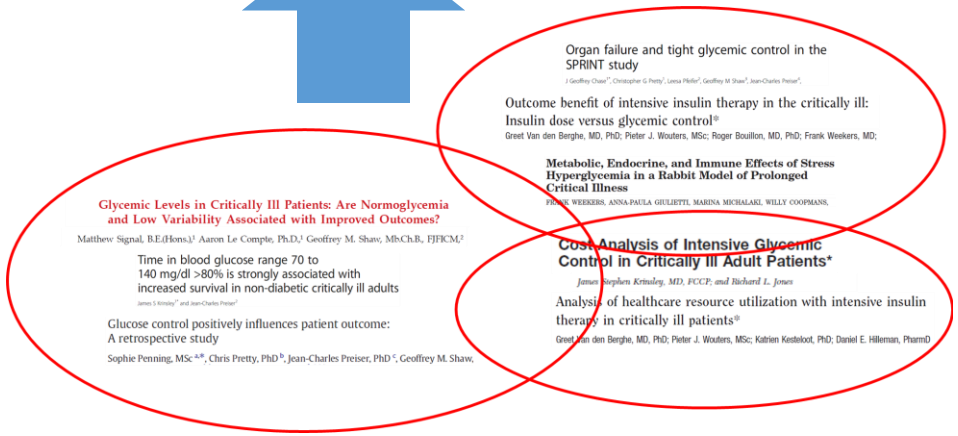


The Balance



The Original Optimism

The New Pessimism



The Real Question: Associations and Causality

Association Between Hyperglycemia and Increased Hospital Mortality in a Heterogeneous Population of Critically Ill Patients

JAMES STEPHEN KRINSLEY, MD

The New Pessimism

- Does GC cause hypos and variability and death, because those who die are more likely to be more resistant, variable and hard to control?

Or …

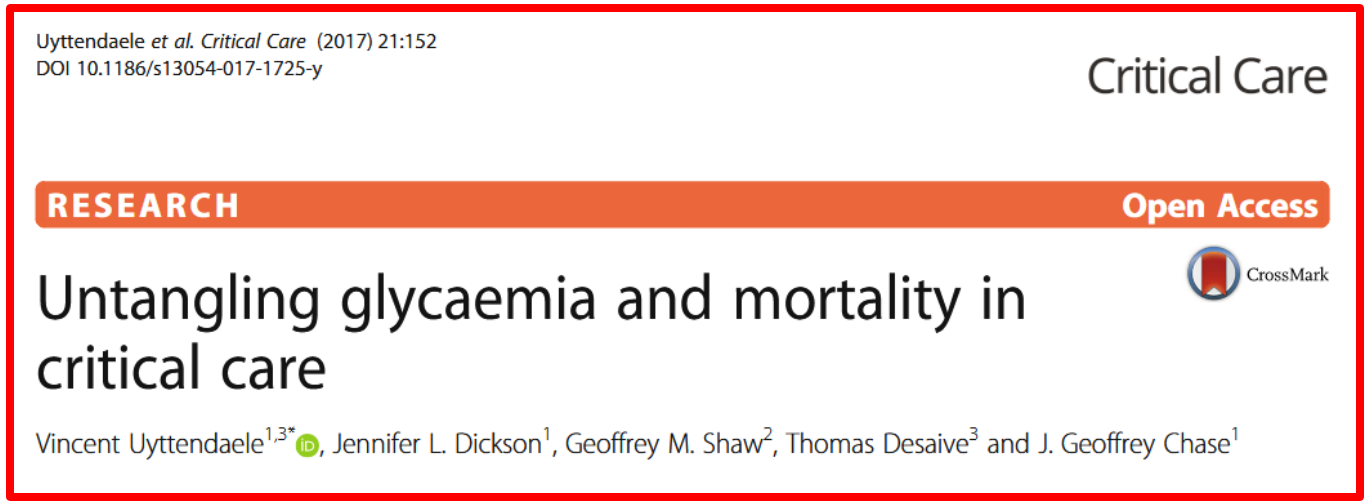
The Original Optimism

- Does good GC cause better outcomes as we expect?

Are Patients Who Die Harder to Control?

- **If yes,** then GC is a bad idea as it creates more hypos and variability, particularly among those more likely to die
  - **The associations are a function of morbidity and eventual mortality – GC offers no benefit and possible harm**

- **If no**, then glycemic level and variability are strictly a function of the GC given (or not), and thus outcomes (and association with mortality) follow from that GC
  - **The associations are caused by poor GC and safe, effective GC reduces morbidity and mortality**



Are Patients Who Die Harder to Control?

- A clinically very well validated (over 50 journal articles) measure of metabolic level (***SI***) and its hour-to-hour variability (***%ΔSI***) in 6-hour blocks over 1st 72 hours
  - ***Compare those who lived with those who died over first 72 hours***
  - ***SI*** → **is insulin resistance the same?**
  - ***%ΔSI*** → **is variability (the hard part of control) the same?**

- Tested for ***statistical <u>difference</u>*** using bootstrapping (most robust means)
  - Are they different?
  - ***Not different (p > 0.05) does NOT mean THE SAME***

- Tested for ***statistical <u>equivalence</u>*** (within one measurement error std deviation)
  - Are they the same (to within measurement error)?

- Equivalent ***SI*** and ***%ΔSI*** in any 6-hour block → not harder to control

No! Dysglycemia → Mortality (not vice versa)

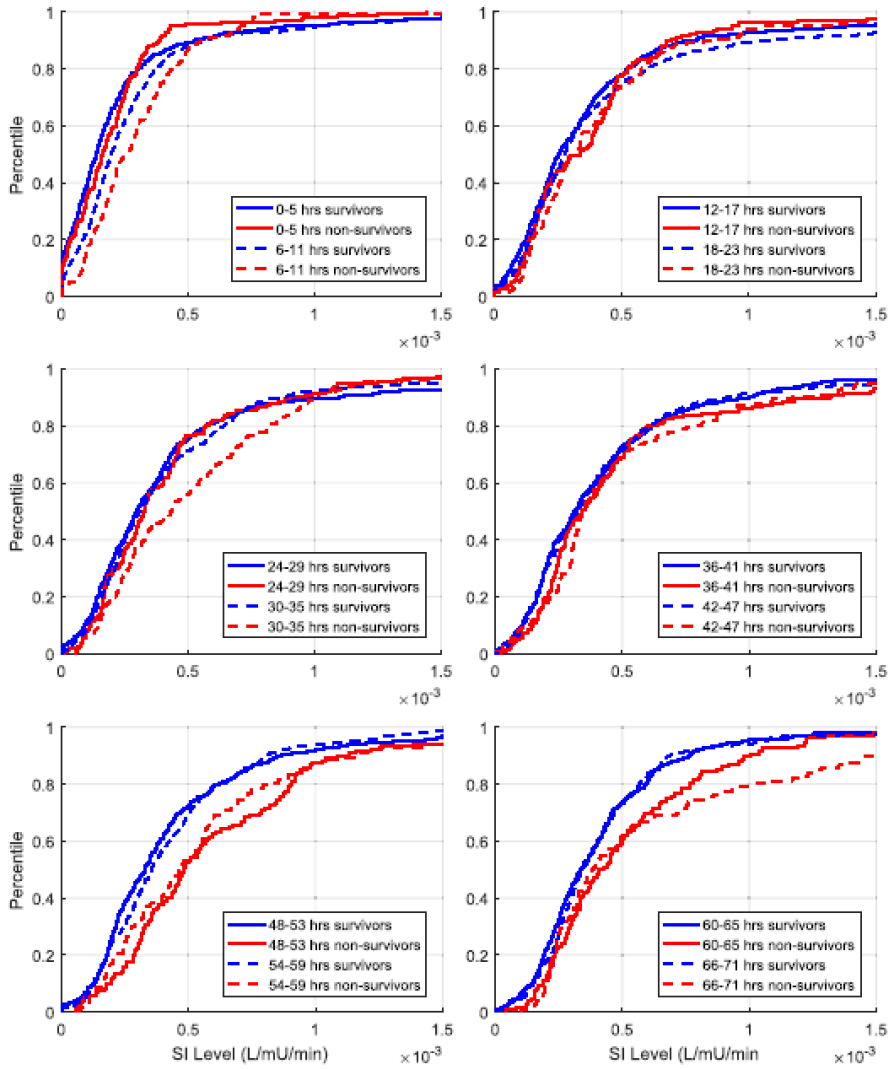


Fig. 3 Cohort 1 cumulative insulin sensitivity (SI) levels over 6-h time intervals for the first 72 h of glycaemic control. At any level of SI, the *y*-axis gives the percentage of SI values (decimal percentile) below this level. The 95% CI on difference in medians was computed using bootstrapping

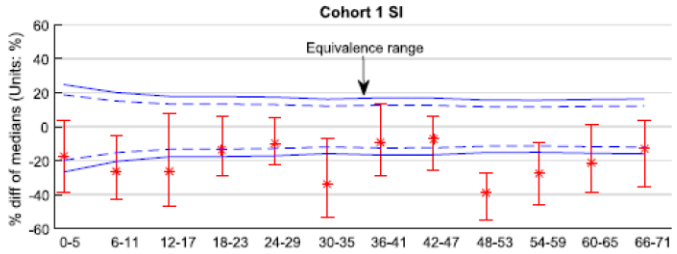


Fig. 4 Equivalence testing on insulin sensitivity (SI) for each 6 h block for Cohort 1 and Cohort 2. The *solid blue lines* give equivalence ranges for 9.4% blood glucose error [58] and the *blue dotted lines* a smaller 7% error reported for the device used in highly controlled tests [105]. Equivalence is accepted if the 95% CI (*bars*) of bootstrapped percentage differences in median SI values is within the equivalence range, and rejected otherwise (×)

- ***SI*** is *rarely* different
- ***SI*** is *never* equivalent
- Those who die have higher ***SI*** than those who live !!
- Those who die are just a little easier to control in level (~0.5 U/hour less insulin for some, but p > 0.05)

No! Dysglycemia → Mortality (not vice versa)

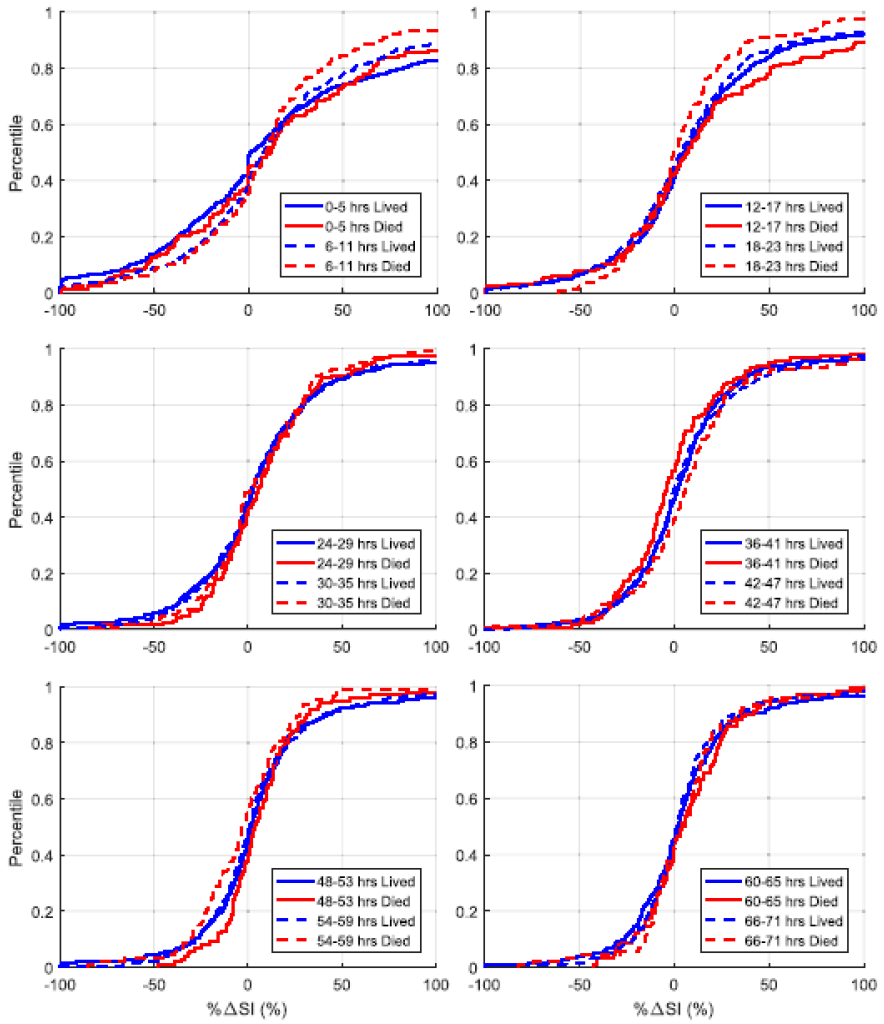


Fig. 6 Cohort 1 cumulative hour-to-hour percentage changes in insulin sensitivity (%ΔSI) over 6-h time intervals for the first 72 h of glycaemic control. At any level of %ΔSI, the *y*-axis gives the percentage of %ΔSI values (decimal percentile) below this level. *p* Values were calculated using the Kolmogorov-Smirnov test

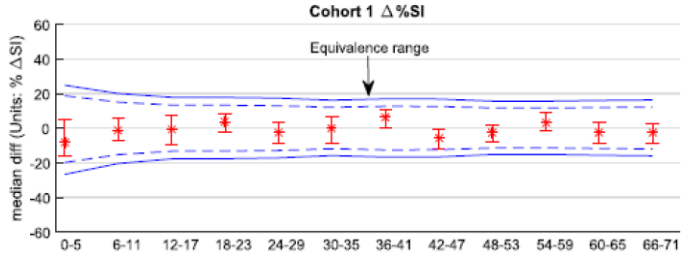


Fig. 7 Equivalence testing on insulin sensitivity variability (hour-to-hour percentage change in insulin sensitivity [%ΔSI]) for each 6-h block for Cohort 1 and Cohort 2. The *solid lines* give equivalence ranges for 9.4% blood glucose error [58], and the *dotted lines* give a smaller 7% error reported for the device used in highly controlled tests [104]. Equivalence is accepted (⇔ in Table 5) if the 95% CI (*bars*) of bootstrapped difference in median %ΔSI are within the equivalence range, and rejected otherwise (×)

- ***%ΔSI*** is *never* different
- ***%ΔSI*** is *always* equivalent
- Variability is equivalent between survivors and non-survivors
- ***No difference in ability to control, and thus should be no difference in hypos, and variability metrics***

Therefore …

- Glycemic control determines outcome (period, end of debate).

Uyttendaele *et al. Critical Care* (2017) 21:152
DOI 10.1186/s13054-017-1725-y

Critical Care

RESEARCH Open Access

Untangling glycaemia and mortality in critical care

Vincent Uyttendaele[1,3*], Jennifer L. Dickson[1], Geoffrey M. Shaw[2], Thomas Desaive[3] and J. Geoffrey Chase[1]

- **But, then, why did the other trials all fail?**
- **For whom is GC beneficial? All patients? Some patients**

All Patients Must Receive *Safe, Effective* GC

Organ failure and tight glycemic control in the SPRINT study

J Geoffrey Chase[1*], Christopher G Pretty[1], Leesa Pfeifer[2], Geoffrey M Shaw[3], Jean-Charles Preiser[4], Aaron J Le Compte[1], Jessica Lin[2], Darren Hewett[1], Katherine T Moorhead, Thomas Desaive[5*]

CRITICAL CARE

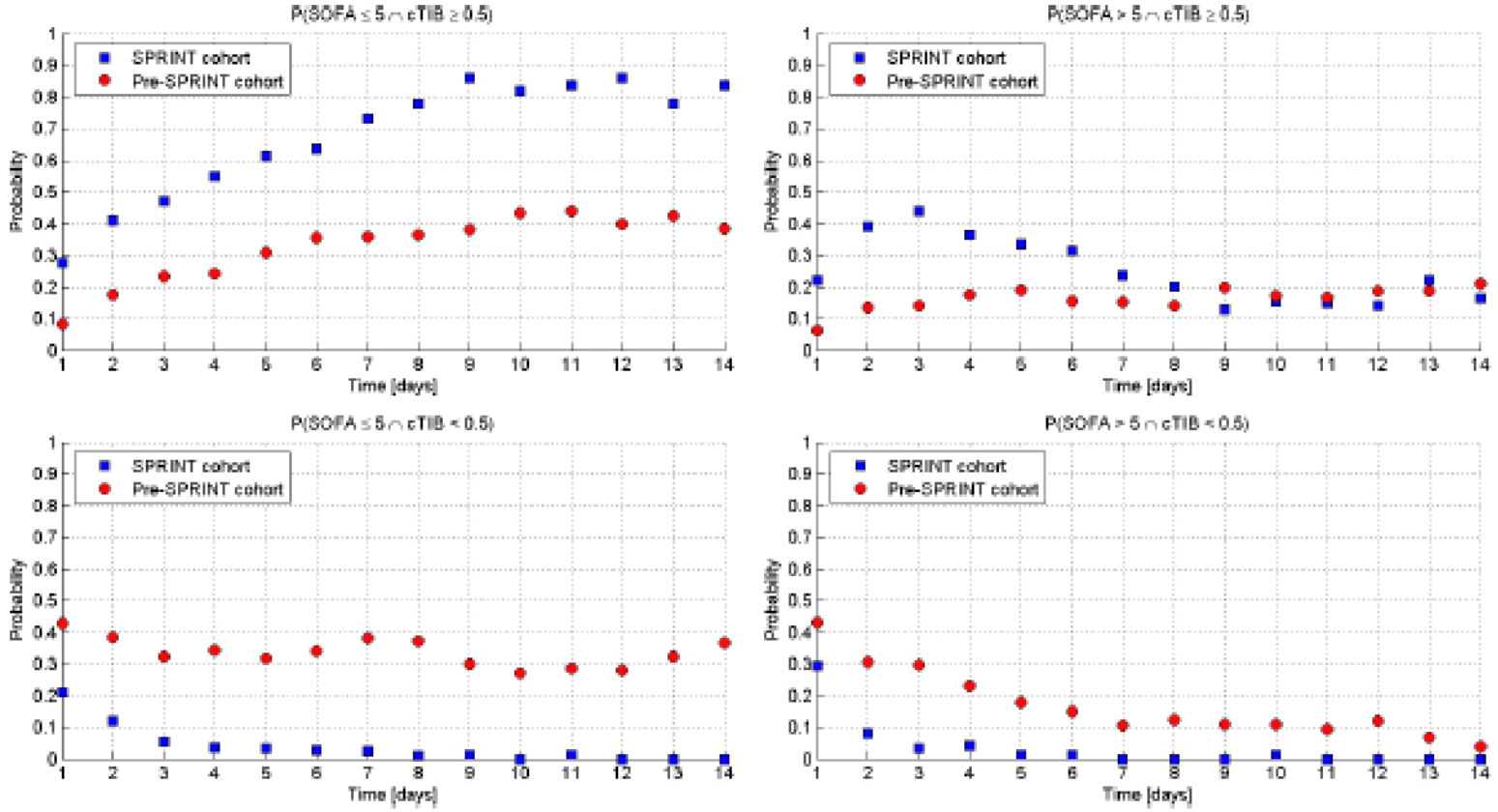


Figure 6 Joint probabilities for all four combinations of SOFA score and cTIB, for both cohorts. Joint probability analysis of SOFA score and cTIB for all four combinations given a SOFA threshold of 5 and a cTIB threshold of 0.5.

- SPRINT achieved >98% of patients with cTIB > 50% within 2.5 days
- ~15% of patients have poor organ failure ***and*** poor GC (bottom right) in retrospective cohort
- If given good control, where do they go?
- No specific patient groups
- ***Thus, all must receive safe, effective control***

Safe, Effective GC For All? (Studies > 100 patients, Standard of Care, …)

A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study
Intensive Care Med
DOI 10.1007/s00134-009-1585-2

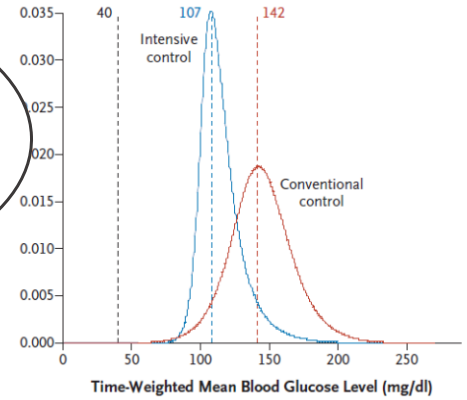
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis
N ENGL J MED 358;2 WWW.NEJM.ORG JANUARY 10, 2008

Intensive versus Conventional Glucose Control in Critically Ill Patients
The NICE-SUGAR Study Investigators*
N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial
Intensive Care Med (2014) 40:171–181

No more than 70-75% (or less) of patients were in the targeted GC band… Covers the likely 15-20% who may benefit and the mortality differences in studies below

Multi-centre trials had highly variable (poorer) control across ICUs



No

(and *MANY* others)

Yes

(+ very few others)

The ONLY studies for >100 patients and full LoS and/or are standard of care

The ONLY study to reduce BOTH mortality and hypoglycemia

Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial
Dubois *et al. Critical Care* (2017) 21:212

Effect of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients
Mayo Clin Proc. • *August 2004;79(8):992-1000*

Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change
Critical Care 2008, 12:R49 (doi:10.1186/cc6868)

Intensive Insulin Therapy in the Medical ICU
N ENGL J MED 354;5 WWW.NEJM.ORG FEBRUARY 2, 2006

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS
N Engl J Med, Vol. 345, No. 19 · November 8, 2001

Safety, efficacy and clinical generalization of the STAR protocol
Stewart *et al. Ann. Intensive Care (2016) 6:24*

Needs (for all patients and ICUs) For Success

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Safety	Performance / Efficacy	Replicability
Minimal to Zero Hypoglycemia	High Time in Band	Same in Every ICU

Effect of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients

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Stewart *et al. Ann. Intensive Care (2016) 6:24*

How? (Many / Most protocols achieve none of these 3 goals)

Personalisation is the key to Safety and Performance

Safety	Performance / Efficacy	Replicability
Minimal to Zero Hypoglycemia	High Time in Band	Same in Every ICU

Effect of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients
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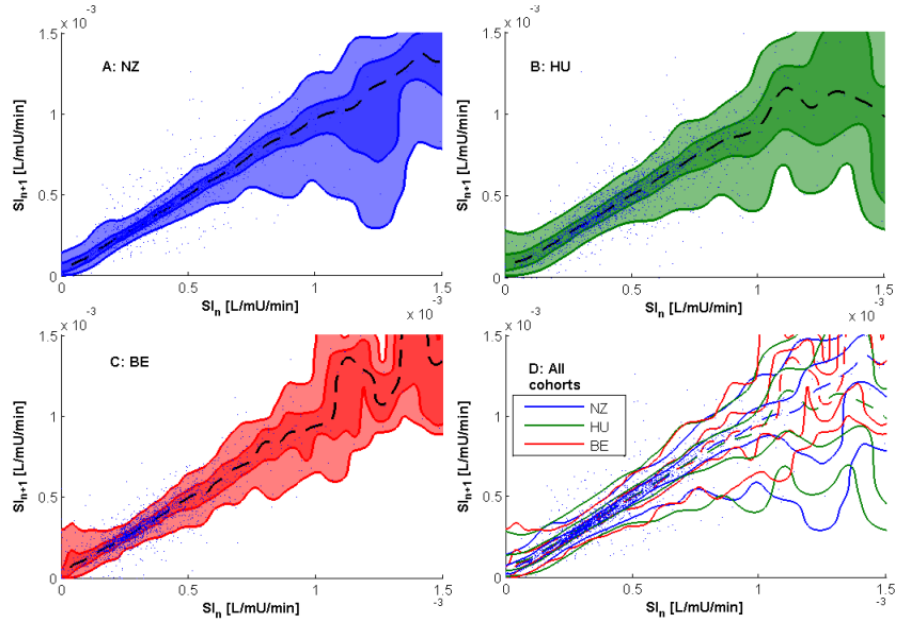
Replicability is hard. Requires personalisation that is not ICU dependent

It also requires compliance to protocol – good interface

Personalised

- STAR ***doses on risk*** and level using a patient-specific insulin sensitivity ***SI***

- ***Risk*** is a function of ***future potential patient variability (%ΔSI)***
  - ***%ΔSI*** has been shown to be consistent across ICUs & cohorts (Dickson, IEEE Trans 2017)
  - A measure of "***How wrong can I be(come)?***"



Generalisability of a Virtual Trials Method for Glycaemic Control in Intensive Care

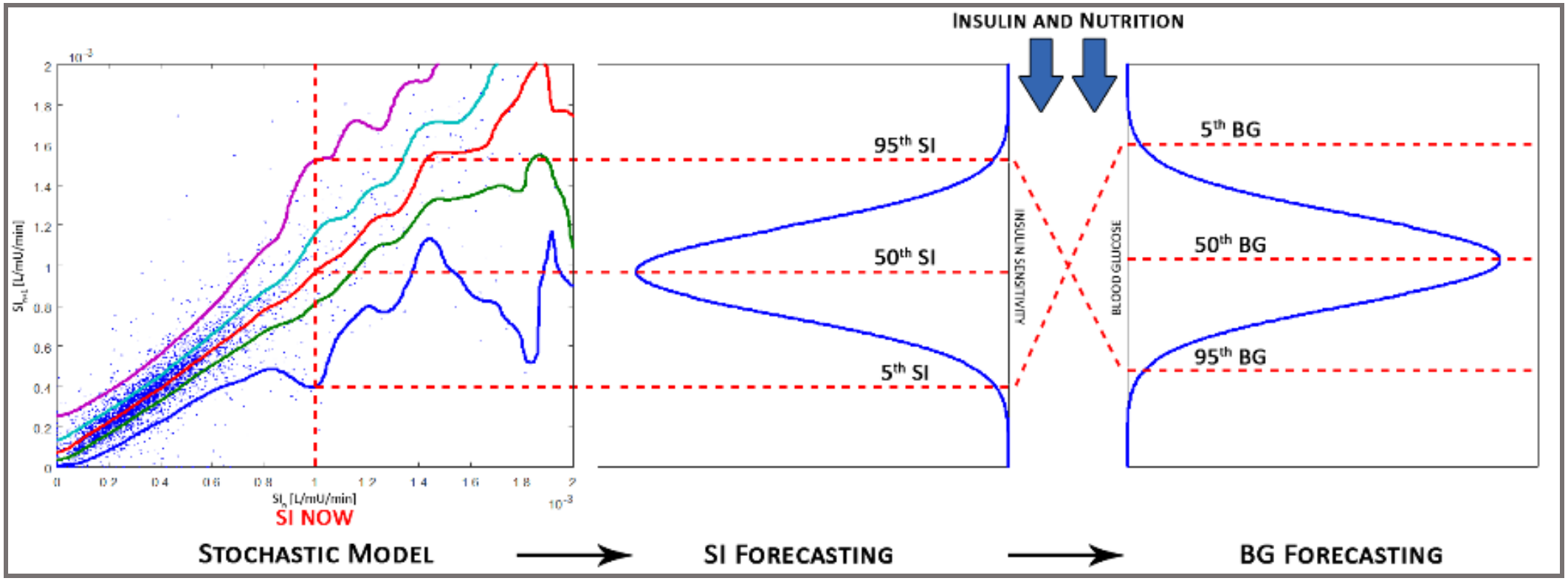
Jennifer L. Dickson, Kent. W. Stewart, Christopher G. Pretty, *Member, IEEE*, Marine Flechet, Thomas Desaive, Sophie Penning, Bernard C. Lambermont, Balázs Benyó, *Member, IEEE*, Geoffrey M. Shaw, J. Geoffrey Chase

TBME-01160-2016

SI can change significantly over 1-3 hours → The root of (all?) GC problems!

Personalised

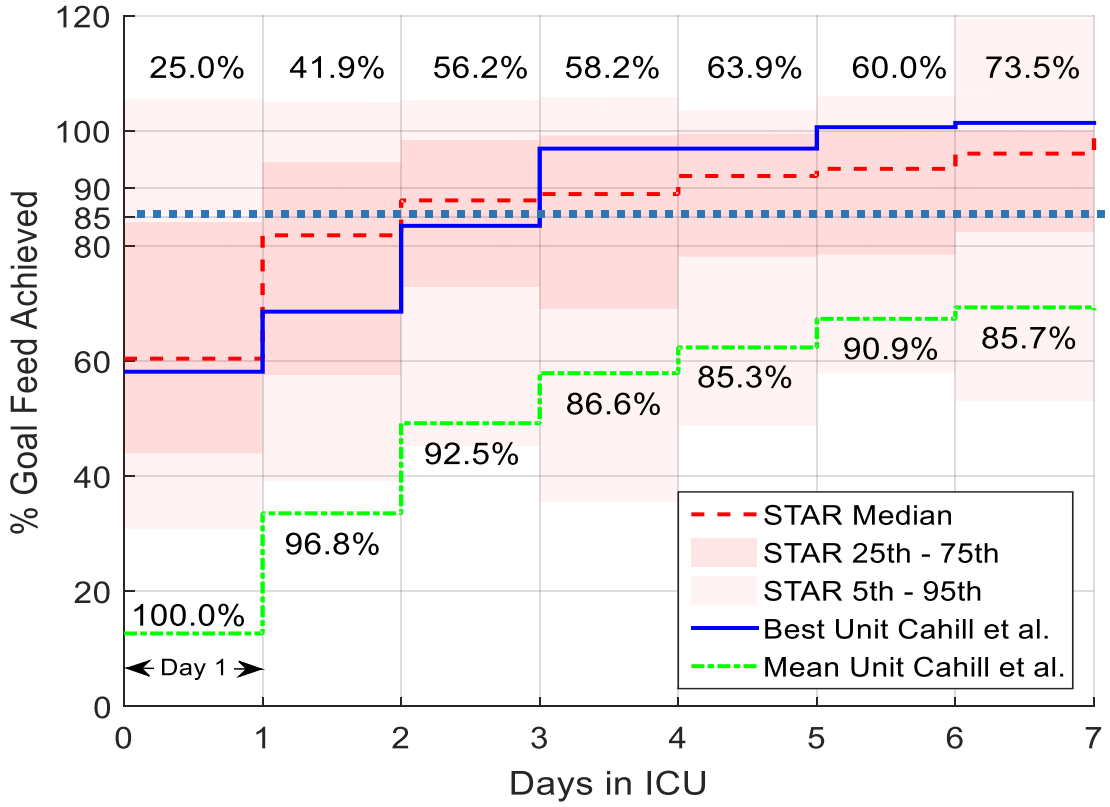
- STAR ***doses on risk*** and level using a patient-specific insulin sensitivity ***SI*** and ***%ΔSI***



Every patient is treated based on their patient-specific (at that time) SI level and their forecast risk of variation in SI → <u>And thus every patient gets equal (good) control</u>

Personalised

- STAR has ***1% hypoglycemia by patient*** and ***84% time in 4.4-8.0 mmol/band***
- ***All*** patients with 24+ hours LoS have ***over 50% time in band***



85% ACCP goal = optimal amount for mortality, based on 158 ICU survey in 21 countries

Nutrition therapy in the critical care setting: What is "best achievable" practice? An international multicenter observational study*

Naomi E. Cahill, RD, MSc; Rupinder Dhaliwal, RD; Andrew G. Day, MSc; Xuran Jiang, MSc;

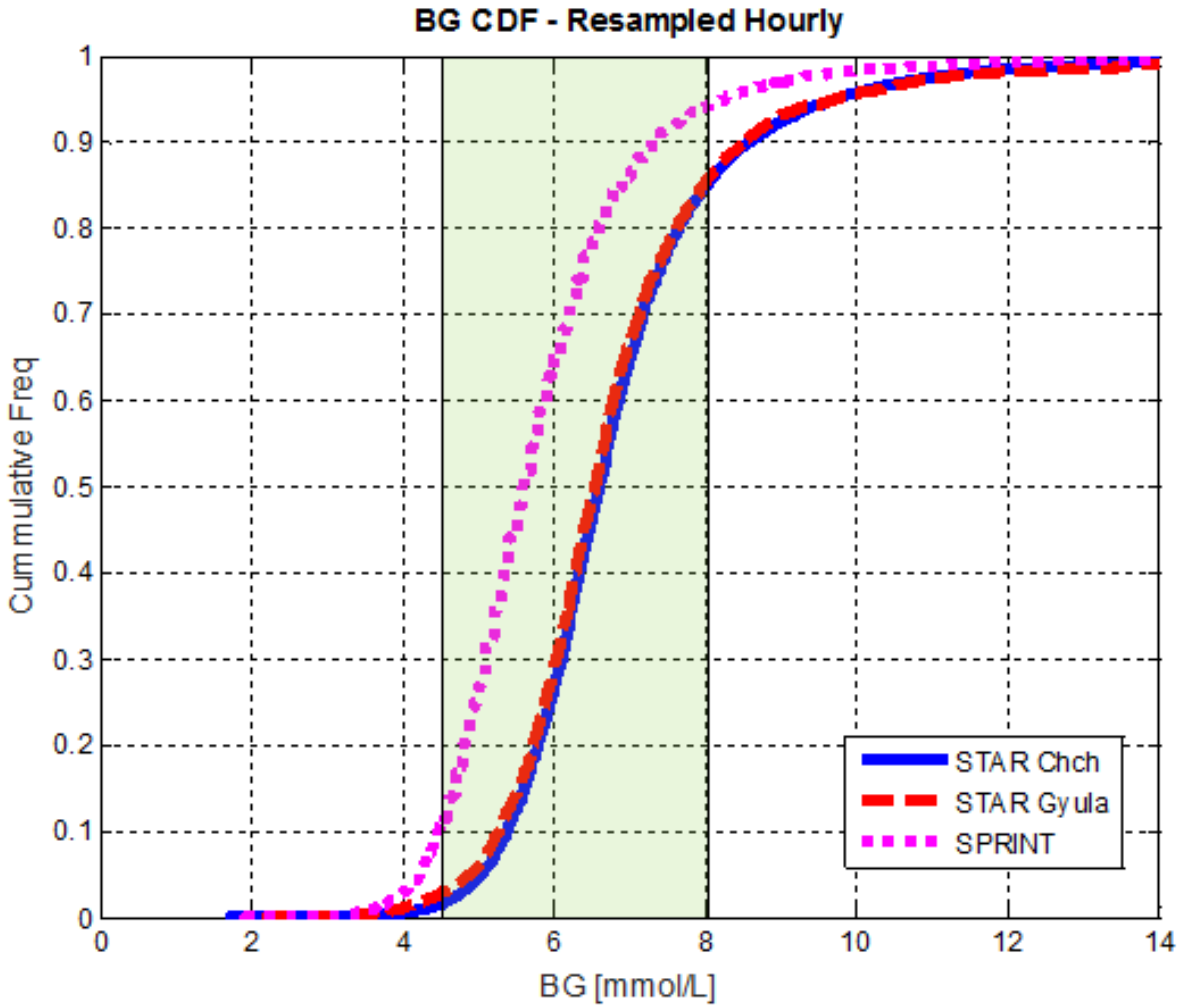
Crit Care Med 2010 Vol. 38, No. 2

Optimal amount of calories for critically ill patients: Depends on how you slice the cake!*

Crit Care Med 2011 Vol. 39, No. 12

Control is world class, nutrition is ~ Best in World from survey of 158 ICUs *(Cahill, 2010; Heyland 2011)*

Personalised → Replicable



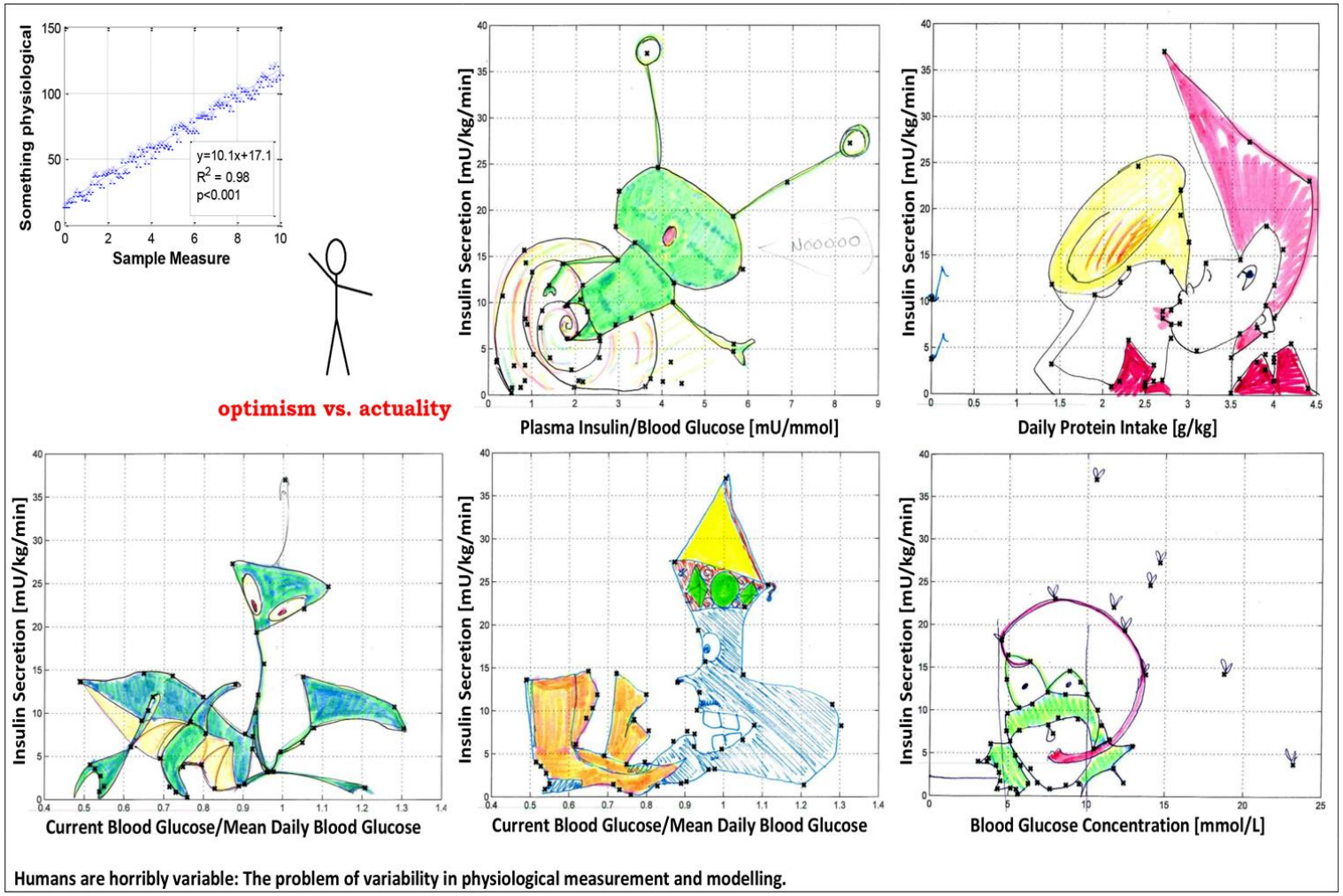
- STAR had identical results in Christchurch and Gyula
- Patients in Gyula were much more ill (APACHE II 28 vs 16)
- STAR had same approach but insulin and nutrition was administered very differently (infusions vs bolus; different nutrition composition, …)

The ability to deliver the same (good) glycemic control despite large differences in patient severity and clinical practice is the key to gaining benefits of GC

Personalised control enables this outcome!

A very short summary

- Humans are horribly variable → Personalised care is the answer



Humans are horribly variable: The problem of variability in physiological measurement and modelling.

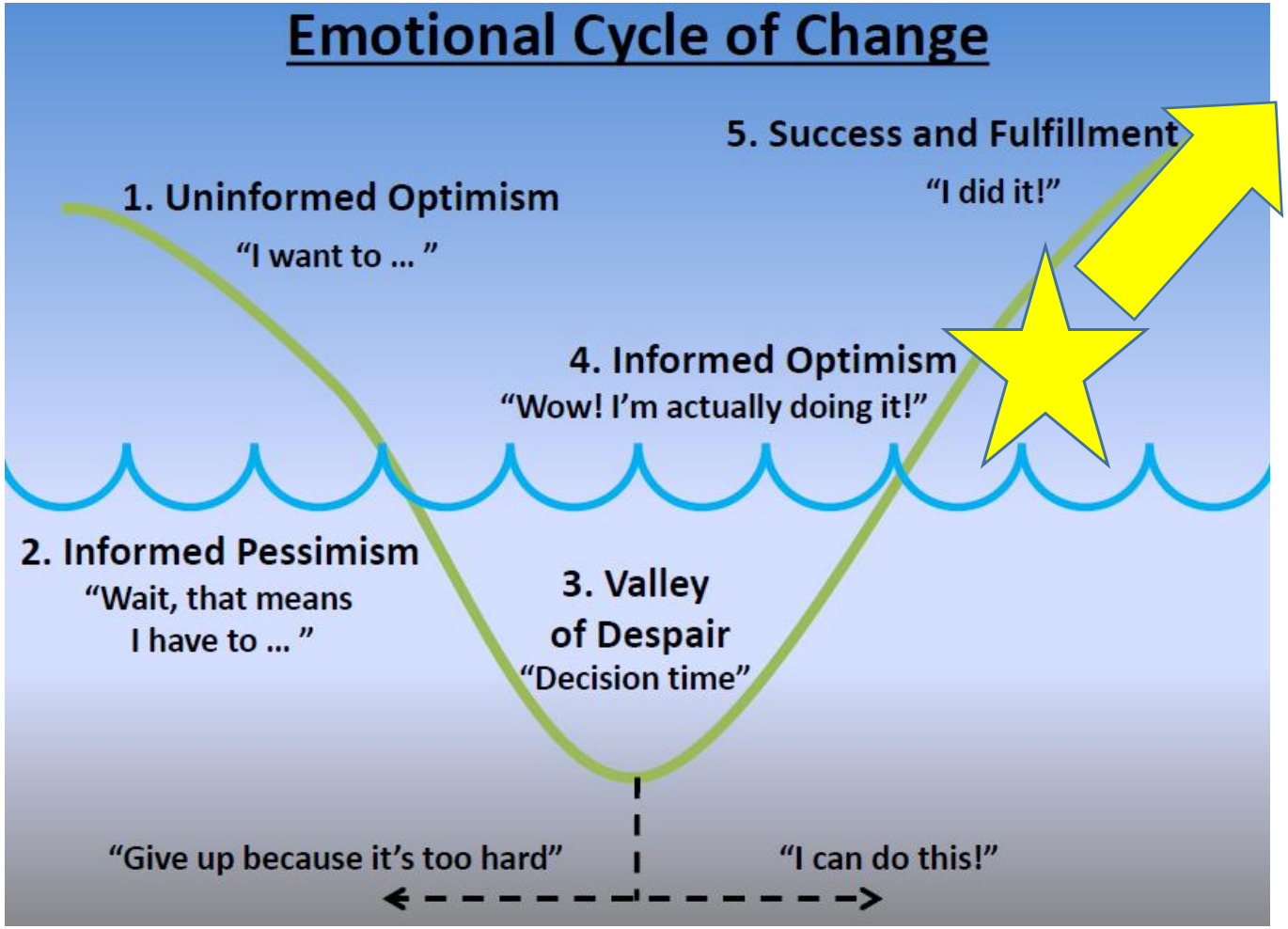

A brief pause for reflection

Conclusions

- Glycemic control can (and does) affect outcomes
- Not controlling BG < 7.0 – 8.0 mmol/L affects morbidity, mortality, and cost
- Ignoring the problem is no longer an option
- Personalisation is the key to safe, effective GC for all – ***One Method Fits All***
  - And an end to ***"One size fits all"*** protocols
- Our goals should be safety, performance, and replicability – we should demonstrate these ***well before*** we implement or engage in a trial, as very few have been able to demonstrate all three criteria.

Talk available at: http://tinyurl.com/ycwwjkvl
All references (30) available at: http://tinyurl.com/yanndo82

Conclusions



Questions (and the path forward)